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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,921	10/31/2005	Hiroshi Miura	280271US0X PCT	2311

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EXAMINER	
PALENIK, JEFFREY T	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)
	10/554,921	MIURA ET AL.
	Examiner	Art Unit
	Jeffrey T. Palenik	1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-35* is/are pending in the application.

4a) Of the above claim(s) *25-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11 Aug. 2010*.	6) ☐ Other: _____.

DETAILED ACTION

STATUS OF THE APPLICATION

Receipt is acknowledged of Applicants' Request for Continued Examination (RCE), Amendments and Remarks, filed 15 July 2010, in the matter of Application N° 10/554,921. Said documents are entered on the record. The Examiner further acknowledges the following:

Claims 21-35 are pending, where claims 25-35 remain withdrawn from consideration.

No claims have been added or cancelled.

Claim 21 has been amended to recite that the composition is suitable for oral administration. Support is provided in the instant disclosure.

No new claims have been added.

The Examiner acknowledges that no new matter has been added to the claims.

Thus, claims 21-24 continue to represent all claims currently under consideration.

INFORMATION DISCLOSURE STATEMENT

One new Information Disclosure Statement (IDS) filed 11 August 2010 is acknowledged and has been considered. It appears that Applicants have submitted a second document for consideration, namely a "Notice of Reasons for Rejection" pertaining to Japanese Application N° 2005-505927. While not listed on the PTO-1449, the Examiner has considered the document. Applicants are respectfully requested to note the document on a subsequent PTO-1449.

WITHDRAWN REJECTIONS

Rejection under 35 USC 103

Applicants' remarks presented in traversal of the obviousness rejections made to claims 21-24, over Verhoff et al. in combination with Takano et al. have been fully considered and are persuasive. Specifically, the remarks distinguish colloidal silica over the presently claimed forms, notably the "colloidal" form is not known in the art as being porous. Further the arguments that Verhoff provides a chemically-induced form of colloidal silica is also persuasively argued, namely because it is the coating applied to the colloidal silica which is made porous rather than the silica itself. As such, the rejection now stands **withdrawn**.

NEW REJECTIONS

In light of the aforementioned withdrawn rejections and the amended base claim, the following rejection(s) are presented:

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Akiyama et al. (US Pre-Grant Publication Nº 2004/0058956) in further view of Takano et al. (USPN 6,753,330; already of record) and as further evidenced by Fuji (MSDS for Silysia).

The instant invention is drawn to a composition comprising an extremely poorly water-soluble drug and a porous silica material. Regarding the dimensional limitation(s) recited in claim 1, pertaining to the porous silica material; until some material difference(s) in the properties of the composition are demonstrated, said limitation is considered by the Examiner to be directed toward the composition, which is instantly claimed. That is, a showing in the art of the claimed composition will be interpreted by the Examiner as reading on Applicants' claimed compounds.

Akiyama et al. teach pharmaceutical compositions comprising a water-poorly soluble or insoluble HER2 inhibitory (interleukin-2) substance, wherein the aqueous solubility of the substance and its absorbability into the blood are improved through incorporation into the dosage forms taught (Abstract; claim 1). Claim 8 further discloses that such a substance will have a solubility of less than 10 mg/mL at 25°C. Paragraphs [0341] and [0348] disclose and define other immune therapeutic agents (e.g., interleukins) whose solubility and absorption into the blood may be improved by the invention of Akiyama. Solid dispersions of the invention which are orally administrable to humans are disclosed ¶[0356]. Said dispersions are further disclosed as containing additives which are preferably taught as including such porous silicas as calcium silicate (e.g., Florite-RE) and light silicic anhydride (e.g., Sylysia) ¶¶[0302]-[0304]. Thus the limitations of claims 21 and 22 are considered to have been met by the reference. The limitations of claim 23 are considered to be read upon by ¶[0328] which states that the preferable weight ratio of the additive such as an excipient (e.g., Florite or Sylysia) to a water-poorly soluble substance is usually in the range of 0.1:1 to 20:1, preferably 0.3:1 to 10:1 and more preferably 1:1 to 3:1.

While Akiyama does preferably disclose that the solubility of water-poorly soluble interleukin-2 substances (e.g., HER2 inhibitory substance) is improved, it is also expressly disclosed that the solubility of other poorly soluble substances may also be improved, namely interleukins, in general. One such active ingredient is 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one, which as evidenced by Takano et al., is a poorly water-soluble interleukin-1β compound. However, Akiyama does not specifically disclose using the instantly claimed interleukin-1β compound. Takano remedies this deficiency.

Takano et al. teach pharmaceutical solid dispersions comprising "compound 1" which is: 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyradazin-3-one (Abstract; claim 2). Said compound is further disclosed as historically having "exceptionally poor solubility in water, and its dissolvability from the pharmaceutical composition is very bad" (col. 1, lines 21-25). Further, as discussed in the Abstract, it is the express goal of the reference to provide compositions containing Compound 1 which have improved dissolvability in water as well as absorption into the blood. Claim 2 also discloses that the formulations will be admixed with a pharmaceutically acceptable carrier, which is further defined as including light anhydrous silicic acid (col. 3, lines 38-40). Example 3, for example, expressly discloses combining two grams of light anhydrous silicic acid with 62 grams of the Compound 1 granules prepared in Example 1. Example 1 discloses that Compound 1 represents 150 grams of the 930 grams of final dried product or about 16.2% of the final product. Thus of the 62 grams of Compound 1 product employed in Example 3, ten grams is attributed to Compound 1. Thus, Example 3 is interpreted as presenting a composition where Compound 1 is in a 5:1 ratio with the silica compound, thereby also meeting the limitations of claim 23. Oral dosage forms such as tablets and capsules are disclosed (e.g., Example 3 and col. 3, lines 48-52).

Given the forgoing teachings which clearly depict the difficulty of interleukin compounds in an aqueous media such as water, a person of ordinary skill in the pharmaceutical arts would have been motivated by the combination of the references to modify (e.g., substitute) the Akiyama composition in order to deliver the interleukin-1β compound of Takano. In view of the disclosed properties for both of the interleukin compounds, it stands to reason that the ordinarily

skilled artisan would have made the substitution with the reasonable expectation that the aqueous solubility and absorbability into the blood of the interleukin-1β compound would have been similarly improved. Further motivation for the substitution is garnered from the claims and Example 3 of Takano wherein a pharmaceutically acceptable carrier, such as light anhydrous silicic acid is also included and in such an amount which reads on the instantly claimed ratio.

Applicants' claimed method limitations set forth in claim 21, wherein the composition is produced by treating a mixture comprising the low water-soluble drug and the porous silicon material with a super- or subcritical carbon dioxide fluid are considered, in light of MPEP §2113, to be immaterial. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) In the instant case, both Akiyama and Takano teach dosage forms which result in the instantly claimed composition wherein the respective purpose of each teaching is to improve the solubility of active ingredients which are naturally poorly-soluble in water. As discussed above, any showing of the porous silica material in the art would be considered by the Examiner to teach the instantly claimed limitations, absent a clear showing of evidence to the contrary. In the instant case, both Akiyama and Takano teach the use of light anhydrous silicic acid (e.g., Silysia). This teaching is considered to meet the recited properties limitations as evidenced by the discussion of the properties of Silysia silica compounds by Fuji (MSDS). Herein, properties for Silysia are disclosed depicting the variability in average pore

diameter as it relates to the size of the particles used to compose the gel. Figures 1 and 2 clearly show that larger particles elicit larger average pore diameters and vice versa. Thus, absent a showing of evidence to the contrary, the property parameters recited in claim 21, which attempt to further define the silica material, would have been well within the purview of the skilled artisan to optimize and achieve, through routine experimentation. Specifically, it would have been within the ability of the ordinarily skilled artisan to adjust the particle size in order to achieve the desired average pore diameter.

Lastly, it is apparent that one of ordinary skill in the art would have had clear motivation to modify Akiyama such that it would improve the delivery of "Compound 1" from its formulations. "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)" "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301.) See MPEP 2144.07.

Thus, based on the combined guidance of the references, the ordinarily skilled artisan would have had a reasonably high expectation in successfully producing the instantly claimed composition. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, alone or in combination, especially in the absence of evidence to the contrary.

All claims have been rejected; no claims are allowed.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner
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